Imaging Genomics Bases of Pediatric Executive Functioning

The University of Pennsylvania

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Grant Number: 1-K01ES25432-01

Periodic rhythms are among the most common patterns in biology. The importance of these rhythms to public health is well documented. Data link circadian disruption to metabolic, cardiovascular, and neoplastic disorders. Yet, interpretation of large-scale data has focused on discrete points in time. New approaches are needed to uncover rhythms in temporally unstructured data and to understand rhythmic physiology. Candidate: Ron Anafi received his MD and PhD in Mechanics from the University of Minnesota. He completed his clinical training in Internal Medicine at the University of Vermont and in Sleep Medicine at the University of Pennsylvania. He is currently an instructor at the Penn. As a research fellow, Dr. Anafi worked with Dr. John Hogenesh on the genomics of circadian rhythms. This proposal builds on Dr. Anafi's strength in developing and applying engineering methods to answer biomedical problems. Environment: The two co-Mentors, Drs. John Hogenesch and Junhyong Kim are leaders in their respective fields. Dr. Hogenesch focuses on the application of high-throughput techniques for the understanding of circadian biology. His work has been a model for data sharing and resource development. Dr. Kim is a Guggenheim and Sloan award-winning scholar whose research is at the intersection of computational biology, algorithms, evolution, and genomics. He has developed algorithms for tree-of-life reconstruction, studied the temporal structure of gene expression, and applied of geometric techniques to the interpretation of biological data. Both have strong records of mentorship and research productivity. Both have excellent working relationships with the PI. Additional support is provided from experts in topology, machine learning, convex optimization, and network modeling. Penn has recently established an institute for Biomedical Informatics and invested in high-performance computing infrastructure. The clinical and research communities are well known, and a new Center for Network Science has been established. Research: Biopsy samples and clinical data from individual patients have no clear temporal ordering. Our work demonstrates that this data contains high dimensional periodic signatures. Once these signatures are discovered, each data point can be aligned to its proper phase. Pooled patient data can be mined for evidence of rhythmic disturbance. The proposal also refines a tool to incorporate prior biological knowledge into the interpretation of rhythmic data. The final aim is to integrate rhythmic metabolomics and expression data onto model metabolic networks. The models will be used to rationally time the administration of drugs and chemotherapeutics. The proposed research, mathematical training, exceptional mentorship, and strong institutional support will enable Dr. Anafi to successfully establish himself as an independent, R01-funded, physician-scientist working at the interface of biological rhythms and big data science. PUBLIC HEALTH RELEVANCE: Periodic rhythms are ever present in biology. Ninety-minute cycles in brain activity, daily oscillations in blood pressure and cholesterol synthesis, and monthly rhythms in hormone production are all important features of physiology. The goal of this grant is to develop techniques to identify rhythmic signatures in large, unstructured data sets, and to extract actionable medical knowledge from those observations. This work will uncover temporal information from clinical records and existing research databases. The data will be used to help determine the best time to administer drug therapies and chemotherapeutics.